

### **REMARKS/ARGUMENTS**

Claims 1-6 and 8-15 are pending in the present application. Claim 7 was previously cancelled.

Claims 1-5 and 9-15 are directed to certain novel compounds. Claim 6 is directed to a pharmaceutical composition comprising the compounds recited in claim 1 or 2. Claim 8 is directed to a method of using the compounds recited in claim 1 or 2 to treat various indications including pain.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as enabling for treating pain, but not enabling for treating all other recited diseases including rheumatic diseases, ileus, obstipation, overweight, and addiction. The Examiner refers to the factors that must be considered in order for the specification to be enabling for what is being claimed. The Examiner states that among the factors that leads to the conclusion that the specification is not enabling is the state of the prior art. A close review of the prior art indicates that compounds with chemical structures close to those presently claimed possess beneficial activity in the treatment of rheumatic diseases, ileus, obstipation, overweight, and addiction. A listing of the relevant prior art references is attached for the Examiner's reference. Accordingly, it is respectfully requested that the rejection of claim 8 under 35 U.S.C. 112, first paragraph, be withdrawn.

Claims 1-5, 8, 9, 11 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner on pages 4-5 of the Office Action offered proposed amendments to certain of the pending claims. These amendments have been incorporated in the present Amendment. Accordingly, it is respectfully request that the rejection of claims 1-5, 8, 9, 11 and 15 under 35 U.S.C. 112, second paragraph, be withdrawn.

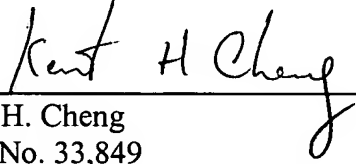
Claim 8 is rejected under 35 U.S.C. 101 as not reciting a process step. Claim 8 is amended to recite a process step. Accordingly, the rejection of claim 8 under 35 U.S.C. 101 has been rendered moot.

Claims 1, 3, 5, 6, 8-10 and 13-15 are rejected under 35 U.S.C. 102(b) as anticipated by H. Schmidhammer et al., *Heterocycles*, vol. 49, 489-497 (1998), as disclosing compounds encompassed by the claims. The Examiner cites to compounds 9, 5 and 10 disclosed by Schmidhammer as anticipating the present claims. We respectfully traverse. The compounds disclosed in Schmidhammer are excluded by the provisos recited at the end of claim 1. Compound 9 requires the substituent at the 3<sup>rd</sup> position to be hydrogen, where as the second proviso of claim 1 excludes such a compound with a hydrogen substituent. Compound 5 requires the substituent at the 3<sup>rd</sup> position to be hydrogen and the substituent at the 4<sup>th</sup> position to be methoxy, where as the third proviso of claim 1 excludes such a compound. Compound 10 requires the substituent at the 3<sup>rd</sup> position to be hydrogen and the substituent at the 4<sup>th</sup> position to be hydroxy, where as the third proviso of claim 1 excludes such a compound. Claims 3, 5, 6, 8-10 and 13-15 are dependent on claim 1, and likewise exclude the compounds disclosed in Schmidhammer. Accordingly, it is respectfully requested that the rejection of claims 1, 3, 5, 6, 8-10 and 13-15 under 35 U.S.C. 102(b) as anticipated by Schmidhammer be withdrawn.

Claims 1, 3- 6, 8, 10-12, 14 and 15 are rejected under 35 U.S.C. 102(b) as anticipated by RN 139450-82-1 in disclosing a compound encompassed by the claims. Claim 1 has been amended to exclude the compound disclosed in RN 139450-82-1 by reciting an additional proviso. Claims 3- 6, 8, 10-12, 14 and 15 are dependent on claim 1, and likewise exclude the same compound. Accordingly, it is respectfully requested that the rejection of claims 1, 3- 6, 8, 10-12, 14 and 15 under 35 U.S.C. 102(b) as anticipated by RN 139450-82-1 be withdrawn.

If any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,  
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## **6-Keto-Indications:**

### **Rheumatic diseases:**

Eisenstein, T.K., and Hilburger, M.E. 1998. Opioid modulation of immune responses: effects on phagocyte and lymphoid cell populations. *J. Neuroimmunol.* 83:36-44.

McCarthy, L., Wetzel, M., Sliker, J.K., Eisenstein, T.K., and Rogers, T.J. 2001. Opioids, opioid receptors, and the immune response. *Drug. Alcohol. Depend.* 62:111-123.

Walker, J.S., Wilson, J.L., Binder, W., Scott, C., and Carmody, J.J. 1997. The anti-inflammatory effects of opioids: their possible relevance to the pathology and treatment of rheumatoid arthritis. *Rheumat. Arth.* 1:291-299.

Walker, J.S., Chandler, A.K., Wilson, J.L., Binder, W., and Day, R.O. 1996. Effect of mu-opioids morphine and buprenorphine on the development of adjuvant arthritis. *Inflamm. Res.* 10:557-563.

Stefano, G.B., Fricchione, G.L., Goumon, Y., Esch, T. 2005. Pain, immunity, opiate and opioid compounds and health. *Med. Sci. Monit.* 11:MS47-53.

### **Ileus:**

Camilleri, M. 2005. Alvimopan, a selective peripherally acting  $\mu$ -opioid antagonist. 2005. *Neurogastroent. Motil.* 17:157-165.

Holzer, P. 2004. Opioids and opioid receptors in the enteric nervous system: from a problem in opioid analgesia to a possible new prokinetic therapy in humans. *Neurosci. Lett.* 361:192-195.

Philippe, D., Dubuquoy, L., Groux, H., Brun, V., Chuoï-Mariot, M.T.V., Gaveriaux-Ruff, C., Colombel, J.-F., Kieffer, B.L., Desreumaux, P. 2003. Anti-inflammatory properties of the  $\mu$  opioid receptor support its use in the treatment of colon inflammation. *J. Clin. Invest.* 111:1329-1338.

### **Obstipation:**

Yuan, C.-S., Wei, G., Foss, J.F., O'Connor, M., Karrison, T., Osinski, J. 2002. Effects of subcutaneous methylnaltrexone on morphine-induced peripherally mediated side effects: a double-blind randomized placebo-controlled trial. *J. Pharmacol. Exp. Ther.* 300:118-123.

De Ponti, F. 2002. Methylnaltrexone Progenics. *Curr. Opin. Invest. Drugs* 3: 614-620.

**Overweight:**

Yeomans, M.R., Gray, R.W. 2002. Opioid peptides and the control of human ingestive behavior. *Neurosc. Biobehav. R.* 26:713-728.

Zhang, J., Frassetto, A., Huang, R.-R.C., Lao, J.Z., Pasternak, A., Wang, S., Metzger, J.M., Strack, A.M., Fong, T.M., Chen, R.Z. 2006. The  $\mu$ -opioid receptor subtype is required for the anorectic effect on an opioid receptor antagonist. *Eur. J. Pharmacol.* 545:147-152.

Kas, M.J.H., Bos, R. van den, Baars, A.M., Lubbers, M., Lesscher, H.M.B., Hillebrand, J.J.G., Schuller, A.G., Pintar, J.E., Spruijt, B.M. 2004. Mu-opioid receptor knockout mice show diminished food anticipatory activity. *Eur. J. Neurosc.* 20:1624-1632.

**Addiction:**

Kenna, G.A. 2005. Pharmacotherapy of alcohol dependence: targeting a complex disorder. *Drug Discov. Today* 2:71-78.